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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,685	06/21/2007	Fabian Model	P193US	9618

93734 7590 07/22/2010

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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
07/22/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/588,685	MODEL ET AL.	
	Examiner	Art Unit	
	STEPHANIE K. MUMMERT	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-22 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-22 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on April 21, 2010 is acknowledged and has been entered. Claim 1 has been amended. Claims 2, 23-30, 32-39 have been canceled. Claims 1, 3-22 and 31 are pending.

Claims 1, 3-22 and 31 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made NON-FINAL to address the New Grounds of Rejection.

Response to Arguments

Applicant's arguments in light of filing a translation of the foreign priority document, see p. 10, filed April 21, 2010, with respect to the rejection of claims as being anticipated by Schatz have been fully considered and are persuasive. The ground of rejection has been withdrawn.

Previous Grounds of Rejection

The rejection of claims 1, 4, 8-9, 11, 14-17 and 31 as being anticipated over Schatz in view of the translation of the foreign priority document as noted above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 10-11, 16-17 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Wong et al. (Cancer Research, 1997, vol. 57: 2619-2622). Wong teaches detection of promoter methylation in p16 in cancer (Abstract).

With regard to claim 1, Wong teaches a method for producing DNA, wherein a methylation analysis is used, comprising the steps of:
a) performing a genome-wide amplification on genomic DNA (p. 2619, col. 2, where whole genome amplification was carried out with PEP amplification, p. 2620, col. 1,), and b) using the amplificates generated in step a) as a standard in the methylation analysis (p. 2619, col. 2, where the amplified products were used in methylation specific PCR reaction).

With regard to claim 3, Wong teaches an embodiment of claim 1 wherein the amplification methods performed are PEP, DOP-PCR or linker PCR (p. 2619, col. 2, where whole genome amplification was carried out with PEP amplification, p. 2620, col. 1).

With regard to claim 10, Wong teaches an embodiment of claim 1 further comprising performing the methylation analysis after conversion of the DNA into a form, in which methylated cytosines can be distinguished from non-methylated cytosines by means of hybridization, by methylation- specific ligation methods, MSP, Heavy Methyl or MethyLight (p. 2619, col. 2, where the amplified products were used in methylation specific PCR reaction, p. 2620. col. 1, where methylation specific PCR is described, see Figure 1).

With regard to claim 11, Wong teaches an embodiment of claim 1 further comprising performing the methylation analysis after conversion of the DNA into a form, in which methylated cytosines can be distinguished from non-methylated cytosines by means of hybridization, by primer extension (p. 2619, col. 2, where the amplified products were used in methylation specific PCR reaction, p. 2620. col. 1, where methylation specific PCR is described, see Figure 1).

With regard to claim 16, Wong teaches an embodiment of claim 1 wherein the methylation analysis is performed for the diagnosis of cancer diseases or other diseases associated with a modification of the methylation status (Abstract, Figure 1, Table 1, where the technique was used to detect methylation in cancer samples).

With regard to claim 17, Wong teaches an embodiment of claim 1 wherein the methylation analysis is performed for the prognosis of desired or undesired effects of drugs and for the differentiation of cell types or tissues, or for the investigation of the cell differentiation (Abstract, Figure 1, Table 1, where the technique was used to detect methylation in cancer samples).

With regard to claim 31, Wong teaches an embodiment of claim 1, wherein the genome-wide amplification is performed by exclusively using nucleotides or nucleotide triphosphates, respectively, which are non-methylated (p. 2620, col. 1, where the genome-wide amplification is carried out using non-methylated nucleotides).

Claims 18-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Adorjan et al. (Nucleic Acids Research, 2002, 30(5):e21, p. 1-9, IDS reference). Adorjan teaches microarray based DNA methylation analysis (Abstract).

With regard to claim 18, Adorjan teaches a method for the determination of methylation rates of DNA samples by means of microarrays containing CG and TG oligomers, comprising the steps of:

a) hybridizing the arrays with two calibration standards, which have defined methylation rates (p. 2, col. 2, where for each analyzed CpG position, CG and TG oligomers are spotted onto a glass array; Table 1, p. 3, col. 2, where DNA fragments of known methylation were mixed in different ratios and hybridized to the array, Figure 1);

b) using the hybridization values of step a) to determine a calibration curve for use as a suitable method of calculation (Figure 1, where the amount of methylation is calculated based on the hybridization and calibration on the array, see p. 3 col. 2); and

c) determining the actual methylation rates of the investigated DNA samples by using this prepared calibration curve (Figure 1, where the amount of methylation is calculated based on the hybridization and calibration on the array, see p. 3 col. 2).

With regard to claim 19, Adorjan teaches an embodiment of claim 18, wherein the two calibration standards have methylation rates of 0% and 100%, respectively (Figure 1, and legend, where the standards have methylation rates between 0 and 100%).

With regard to claim 20, Adorjan teaches an embodiment of claim 18, wherein more than two calibration standards are used, which have different methylation rates (Figure 1, and legend, where the standards have methylation rates between 0 and 100%).

With regard to claim 21, Adorjan teaches an embodiment of claim 18, wherein the actual methylation rates are determined in a multi-stage calculation process, comprising the steps of:
a) normalizing the hybridization values, wherein methylation signals are determined (p. 3, col. 1, where the statistical analysis is described, including the algorithms used, p. 3, col. 2, where the process of detecting and calibrating and normalizing the signals to correlate signals with degree of methylation, see Figure 1 and legend),
b) normalizing the methylation signals with the aim of variance stabilization (p. 3, col. 1, where the signals are normalized using a Support Vector Machine (SVM) and Sequential Minimal Optimization Algorithm, p. 3 col. 2, where the process of detecting and calibrating and normalizing the signals to correlate signals with degree of methylation, see Figure 1 and legend), and
c) determining the methylation rates by using the calibration standards and a suitable maximum likelihood algorithm (Figure 1, where the amount of methylation is calculated based on the hybridization and calibration on the array, see p. 3 col. 1-2, see above).

With regard to claim 22, Adorjan teaches an embodiment of claim 21, further comprising a step prior to step a) wherein the hybridization values are corrected for the background noise

inherent in the measurement method (p. 3, col. 1, where the signals are normalized using a Support Vector Machine (SVM) and Sequential Minimal Optimization Algorithm, p. 3 col. 2, where the process of detecting and calibrating and normalizing the signals to correlate signals with degree of methylation, see Figure 1 and legend).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (Cancer Research, 1997, vol. 57: 2619-2622) as applied to claims 1, 3, 10-11, 16-17 and 31 above and further in view of Adorjan et al. (Nucleic Acids Research, 2002, 30(5):e21, p. 1-9).

Wong teaches all of the limitations of claims 1, 3, 10-11, 16-17 and 31. Wong does not teach the use of a microarray. Adorjan teaches microarray based DNA methylation analysis (Abstract).

With regard to claim 12, Adorjan teaches an embodiment of claim 1 further comprising performing the methylation analysis after conversion of the DNA into a form, in which methylated cytosines can be distinguished from non-methylated cytosines by means of hybridization, by an amplification and a hybridization of the amplificates at oligomer microarrays (p. 2, col. 2, where for each analyzed CpG position, CG and TG oligomers are

spotted onto a glass array; Table 1, p. 3, col. 2, where DNA fragments of known methylation were mixed in different ratios and hybridized to the array, Figure 1; see also p. 2, col. 2, where bisulfite conversion and amplification are discussed.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Wong to include the analysis of methylation using microarrays as taught by Adorjan to arrive at the claimed invention with a reasonable expectation for success. As taught by Adorjan, "We have developed the first microarray-based technique which allows genome-wide assessment of selected CpG dinucleotides as well as quantification of methylation at each site. Several hundred CpG sites were screened in 76 samples from four different human tumour types and corresponding healthy controls. Discriminative CpG dinucleotides were identified for different tissue type distinctions and used to predict the tumour class of as yet unknown samples with high accuracy using machine learning techniques". Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Wong to include the analysis of methylation using microarrays as taught by Adorjan to arrive at the claimed invention with a reasonable expectation for success.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (Cancer Research, 1997, vol. 57: 2619-2622) as applied to claims 1, 3, 10-11, 16-17 and 31 above and further in view of Tost et al. (Nucleic Acids Research, 2003, 31(9):e50, p. 1-10).

With regard to claim 13, Tost teaches an embodiment of claim 1 further comprising performing the methylation analysis after conversion of the DNA into a form, in which

methylated cytosines can be distinguished from non-methylated cytosines by means of hybridization, by means of a multiplex PCR (p. 6, col. 2, where the CpG methylation was detected using multiplex primer extension).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Wong to include the analysis of methylation using multiplex amplification as taught by Tost to arrive at the claimed invention with a reasonable expectation for success. As taught by Tost, "Calibration curves were recorded for simplex, duplex and triplex analysis. For multiplex analysis only extension primers were chosen that did not overlap in their sequence". Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Wong to include the analysis of methylation using multiplex amplification as taught by Tost to arrive at the claimed invention with a reasonable expectation for success.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14-15 rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (Cancer Research, 1997, vol. 57: 2619-2622) as applied to claims 1, 3, 10-11, 16-17 and 31 above and further in view of Guilleret et al. (Int. J. Cancer, 2002, 101, p. 335-341). Wong teaches detection of promoter methylation in p16 in cancer (Abstract).

With regard to claim 14, Guilleret teaches an embodiment of claim 1 wherein a mixture of methylated and non-methylated DNA is used as a standard (Figure 1, where mixtures of methylated and unmethylated plasmid DNA was used as a standard; see also p. 336, col. 1, 'plasmids' heading, where the mix of methylated and unmethylated is discussed).

With regard to claim 15, Guilleret teaches an embodiment of claim 1 wherein several mixtures of methylated and non-methylated DNA with different shares of methylated and non-methylated DNA are used as a standard (Figure 1, where mixtures of methylated and unmethylated plasmid DNA was used as a standard and where the mix included 0%, 50% and 100% methylation; see also p. 336, col. 1, 'plasmids' heading, where the mix of methylated and unmethylated is discussed).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Wong to include the mixtures of methylated and non-methylated DNA as a standard as taught by Guilleret to arrive at the claimed

invention with a reasonable expectation for success. While Wong teaches the use of methylated controls and unmethylated controls, Wong does not teach mixing the controls for detection of different types of methylation, such as differential methylation. As taught by Guilleret, "Unmethylated and methylated plasmids were mixed at different ratios. The bisulfite modification was performed on fully methylated and unmethylated plasmids as well as on different mixes" (p. 336, col. 1). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Wong to include the mixtures of methylated and non-methylated DNA as a standard as taught by Guilleret to arrive at the claimed invention with a reasonable expectation for success to achieve reliable detection of methylation.

Claims 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wong et al. (Cancer Research, 1997, vol. 57: 2619-2622) as applied to claims 1, 3, 10-11, 16-17 and 31 above and further in view of Apgar et al. (Human Immunology, 2003, 64(10), Suppl. 1, p. S86, Abstract). Schatz teaches methylation analysis using mass spectrometry analysis (Abstract).

With regard to claim 4, Apgar teaches an embodiment of claim 1, wherein the amplification method performed is a multiple displacement amplification (MDA) (Abstract, lines 4-6, where the amplification is by MDA).

With regard to claim 5, Apgar teaches an embodiment of claim 4, further comprising using a phi 29 polymerase (Abstract, line 5).

With regard to claim 6, Apgar teaches an embodiment of claim 4, further comprising using a commercially available kit (Abstract, line 10).

With regard to claim 7, Apgar teaches an embodiment of claim 6, wherein the commercially available kits are "GenomiPhi" (Amersham Biosciences) or "Repli-g" (Molecular Staging) (Abstract, line 10).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Schatz to include the GenomiPhi kit of Apgar to arrive at the claimed invention with a reasonable expectation for success. As taught by Apgar, "replicate aliquots of dilute DNA were amplified by MDA using a GenomiPhi kit" (Abstract, line 10). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Schatz to include the GenomiPhi kit of Apgar to arrive at the claimed invention with a reasonable expectation for success.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Dean et al. (US Patent 6,617,137 September 2003) teaches methods of whole genome amplification.

Response to Arguments

Applicant's arguments filed April 21, 2010 have been fully considered but they are not persuasive.

Applicant traverses the rejection of claims 1, 3-22 and 31 as being anticipated by Wong. Applicant argues that Wong "discloses that samples are first treated with bisulfite and then the modified samples are amplified with PEP… therefore, Wong does not disclose feature a) of

claim 1" (p. 8 of remarks). Applicant goes on to argue that "Wong uses PEP in order to reduce the amount of DNA necessary for the assay and not for use as standard". Applicant concludes "Wong cannot use the PEP amplified DNA samples as standard according to the present invention due to the fact that the amplificates are already modified by bisulfite" (p. 9 of remarks).

These arguments have been considered, but are not persuasive. While applicant's arguments regarding the bisulfite modification of the DNA are noted, it is noted in response that the DNA of Wong is still genomic DNA, even if it has been previously modified by bisulfite treatment. While the specification exemplifies the method as requiring amplification of genomic DNA, followed by bisulfite sequencing and analysis of methylation, contrary to Applicant's arguments, the claims do not exclude bisulfite modification of the genomic DNA in either step of the method. Step a) of claim 1 only requires that genomic DNA is amplified by a whole genome amplification. It does not require that the genomic DNA is unmodified. Next, step b) of claim 1 only requires that the amplificates are used as a standard in a methylation analysis, not that the amplificates are bisulfite modified prior to methylation analysis. Furthermore, while Applicant argues that Wong does not teach the use of amplificates as "standards", the claim does not clearly establish how a sample is used as a standard.

Next, it is again noted, as stated in the art rejection above, Wong clearly teaches that it is genomic DNA that is bisulfite modified and amplified by whole genome amplification, see the materials and methods on p. 2620, col. 1, where genomic DNA was extracted from the samples, these samples were modified and amplified by PEP amplification, followed by methylation analysis. Next, it is clearly shown that the products of the amplification were used in further

methylation analysis and also that samples were also included as controls for both methylated DNA and unmethylated DNA (see p. 2620, col. 2 and Figure 1A and B). Therefore, in the absence of limitations in the claims which clearly distinguish over the teachings of Wong, the rejections are maintained.

Applicant traverses the rejection of claims as being anticipated by Adorjan. Applicant argues that they "have amended claim 18 to reflect use of the genomic non-methylated DNA according to claim 1 of the invention as a calibration standard mentioned in step a) of claim 18" (p. 9 of remarks).

These arguments have been considered, but are not persuasive. First, it is noted that the argued amendments to claim 18 are not present in the claims as submitted. Next, it is noted that claim 18 does not depend on claim 1 and also that claim 1 does not produce only "genomic non-methylated DNA". Instead, claim 1 is directed only to the amplification of genomic DNA, which includes both methylated and unmethylated DNA. Therefore, for at least these reasons, these arguments are not persuasive and the rejections are maintained.

Applicant traverses the rejection of claim 12 as being obvious over Wong in view of Adorjan. Applicant argues that "there is no teaching or suggestion in Wong that genomic DNA was amplified via PEP or other WAG methods in order to use its amplificates as standards in the methylation analysis". Applicant also argues that "Adorjan fails to cure all the deficiencies of Wong with respect to claim 1" (p. 11 of remarks).

These arguments have been considered, but are not persuasive for the same reasons as asserted above regarding Wong and regarding Adorjan. As argued above, Wong does provide explicit teaching of amplification of genomic DNA, even if the genomic DNA is bisulfite-modified before amplification. Further, Wong teaches the use of these samples as standards in methylation analysis. Therefore, for at least these reasons, Applicant's arguments are not persuasive and the rejections are maintained.

Applicant traverses the rejection of claim 13 as obvious over Wong in view of Tost. Applicant again reiterates the same arguments as asserted above regarding Wong. These arguments are not persuasive for the same reasons as asserted above and the rejection is maintained.

Conclusion

No claims are allowed. All claims stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephanie K. Mummert/
Primary Examiner, Art Unit 1637

SKM